IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 6653
SCHENK, Dale B.	Examiner: K. Ballard, Ph.D.
Application No.: 09/724,319	Art Unit: 1649
Filed: November 27, 2000	DECLARATION OF DR. PETER SEUBERT UNDER 37 C.F.R. §1.131
For: PREVENTION AND TREATMENT OF AMYLOIDOGENIC DISEASE	

Commissioner for Patents
P.O. Box 1450
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Sir:

I, Peter Seubert, state as follows:

1. My current position is Vice President, Neurodegenerative Research at Elan Pharmaceuticals, Inc., the assignee of the above-captioned application. A copy of my curriculum vitae is attached.

2. I understand that Solomon, US Patent No. 5,688,651 reports that an antibody designated AMY-33 has a putative epitope between residues 25-28 of Aβ. I understand this putative assignment is based on AMY-33 being raised against a 1-28 fragment of Aβ, and Yankner et al., Science 250:279-282 (1990) having speculated that residues 25-35 of Aβ mediated toxic effects. The putative epitope 25-28 represents the intersection of the fragment generating AMY-33 with the 25-35 toxic region hypothesized by Yankner et al.

3. I or others acting under my supervision have performed the following experiment to determine the epitope specificity of the AMY-33 antibody. We obtained the antibody from Zymed Laboratories, Inc (now Invitrogen).

4. The following peptides were used for analysis. Aβ1-10 C-terminally biotinylated obtained from Mimotopes; Aβ1-16 N-terminally biotinylated obtained from Anaspec; Aβ 13-28 biotinylated through a C-terminal cysteine using Pierce's no weigh maleimide PEO2-Biotin at a 10 M ratio; and, Aβ 1-38 biotinylated using Pierce's NHS PEO2 Biotin at a 5 M ratio following ForteBio's recommended biotinylation protocol. Binding was detected using a Fortebio's Octet, which is a label-free instrument for determining both binding and kinetics of protein-protein interactions. For this experiment, the Fortebio Strepavidin High binding FA Biosensors were loaded with 5 μg/ml of the different biotinylated Aβ peptides. The sensors were then allowed to reach baseline before the association and dissociation and K_D of each antibody was determined. Antibodies were run at molar concentrations of 1-10 times their expected K_D. Various antibodies whose epitope specificity had previously been determined, specifically 2H3 (epitope =Aβ2-7) and 12A11 (epitope =Aβ3-7), were used as a positives control for various n terminal peptides and Aβ 1-38: antibody 266 (epitope =Aβ16-23) was used as the positive control for 13-28 and 6H9(epitope Aβ19-22) was used as the positive control for Aβ17-28.

5. The table below shows the measured affinity of AMY33 for the various fragments of Aβ tested. In brief, AMY33 showed binding to Aβ 1-10, 1-16 and 1-38 at approximately 100 fold less affinity than the control antibody 12A11 but showed no detectable binding to Aβ13-28 and 17-28.

		BINDING AFFINITY				
		K_D Aβ 1-10	**K_D Aβ 1-16**	**K_D Aβ 1-38**	**K_D Aβ 13-28**	**K_D Aβ 17-28**
ANTIBODY	**AMY 33**	100-300 nM	100-300 nM	100-300 nM	No binding	No binding
	12A11	Not done	1-2 nM	1-3 nM	No binding	No binding
	2H3	0.6 nM	0.2 nM	0.45 nM	Not done	Not done
	266	Not done	Not done	Not done	0.15 nM	Not done
	6H9	Not done	Not done	Not done	0.6 nM	Not done

6. I conclude from the detectable binding to Aβ1-10 and lack of detectable binding to the Aβ13-28 fragment that the epitope bound by AMY-33 does not lie within residues 13-28 of Aβ.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Peter Seubert

Date: October 11, 2007

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EDUCATION

1984 **Ph.D., Biochemistry**, University of California, Davis
Dissertation Title: Functional studies of ATP sulfurylase from *Penicillium chrysogenum*
Advisor: Dr. Irwin H. Segel

1979 **B.S., Biochemistry**, University of California, Davis

SCIENTIFIC BACKGROUND

1989-present **Vice President Biology Research**, Elan Pharmaceuticals, South San Francisco, California.
Discovery and development of biochemical tests for the diagnosis of Alzheimer's disease. Studies of the metabolism and aberrant deposition of the amyloid protein and microtubule associated protein tau. Characterization of inhibitors of amyloid formation in neuronal culture and transgenic mouse model of Alzheimer's disease. Development of vaccine-based approach to Alzheimer's disease treatment.

1988-1989 **Scientific Consultant**, Cortex Pharmaceuticals, Inc., Irvine, California.

1985-1989 **Postdoctoral Fellow and Assistant Researcher**, Bonney Center for the Neurobiology of Learning and Memory, University of California, Irvine; laboratory of Dr. Gary Lynch. Investigation of the role of calcium-activated proteases in memorial and pathological neuronal events. Demonstration of intracellular proteolysis of brain spectrin coupled to activation of NMDA receptors during ischemia and in response to toxins, lesions, and in certain hereditary disorders. Biochemical studies of roles of calcium activated proteins (calpain, protein kinase C, calmodulin) in neuronal plasticity and degeneration.

proteins (calpain, protein kinase C, calmodulin) in neuronal plasticity and degeneration.

1979-1984 **Graduate Student**, Department of Biochemistry and Biophysics, University of California, Davis. Studies of sulfate activating enzymes: ATP sulfurylase and adenosine 5'-phosphosulfate kinase. Initial velocity, product inhibition, inhibition by substrate analogs, analysis of reaction progress curves by a simplified integrated rate equation, alternative substrates, and equilibrium binding studies used to deduce kinetic mechanisms and ligand binding order of the sulfate activating enzymes.

1978-1979 **Undergraduate Student**, Department of Biochemistry and Biophysics, University of California, Davis; under direction of Dr. Irwin H. Segel. Isolation and preliminary characterization of ATP sulfurylase from mammalian source and thermophilic fungus for comparative studies with mesophilic fungus enzyme.

AWARDS AND HONORS

- National Institute on Aging Postdoctoral Training Fellowship 1985
- Jastro-Shields Research Scholarship Awards 1978, 1979, 1982, 1983
- University of California Regents' Fellowship 1982
- Earl C. Anthony Fellowship 1981
- Outstanding Teaching Assistant in Biochemistry Award 1981
- Henry A. Jastro Scholar in Biochemistry Award 1980
- Andrew Christensen Scholarship 1979
- Outstanding Undergraduate Achievement in Biochemistry Citation 1979
- Graduation with high honors, University of California, Davis 1979

PUBLICATIONS

1. Farley, J.R., Christie, E.A., Seubert, P.A., and Segel, I.H. (1979) Adenosinetriphosphate sulfurylase from *Penicillium chrysogenum*: Evidence for essential arginine, histidine and tyrosine residues. J. Biol. Chem., 254:3537-3542.

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5. Renosto, F., Seubert, P.A., Knudson, P., and Segel, I.H. (1985) APS kinase form *Penicillium chrysogenum*: dissociation and reassociation of subunits as the basis of the reversible heat inactivation. J. Biol. Chem., 260:1535-1544.

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proteolysis (R.L. Mellgren and T. Murachi, eds.) CRC Press, Boca Raton, 251-264.

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ABSTRACTS

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